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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/EP96/05020</p> <p>(22) International Filing Date: 11 November 1996 (11.11.96)</p> <p>(30) Priority Data: 9523752.5 21 November 1995 (21.11.95) GB</p> <p>(71) Applicant (for all designated States except GB JP US): PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A. [BE/IE]; La Touche House, International Financial Services Centre, Dublin 1 (IE).</p> <p>(71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).</p> <p>(71) Applicant (for JP only): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MACRAE, Ross, James [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). SMITH, Janet, Sarah [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).</p>		<p>(74) Agents: HAYLES, James, Richard et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).</p> <p>(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: PHARMACEUTICAL FORMULATIONS</p> <p>(57) Abstract</p> <p>The invention provides a controlled-release pharmaceutical formulation for oral administration consisting essentially of: an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tableting excipients; and optionally one or more enteric polymers. Formulations according to the invention produce a constant rate of release of drug in <i>in vitro</i> models of the gastrointestinal tract.</p>		

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### Pharmaceutical formulations

This invention relates to controlled-release oral pharmaceutical formulations.

- 5    Controlled-release oral pharmaceutical formulations are known. Their purpose is to modify the rate of drug release, for example to produce a constant rate of release of a drug into the gastrointestinal tract of a patient, or to delay the release of a drug into the gastrointestinal tract of a patient (see 'Sustained and Controlled Release Drug Delivery Systems', pp 3-6, edited by J R Robinson, published by Marcel Dekker Inc).

10

US Patent N° 4,765,989 discloses an osmotic delivery device for delivering *inter alia* nifedipine or doxazosin. It has a perforated semipermeable wall enclosing a drug composition which includes an osmopolymer, and a pusher composition containing a second osmopolymer. The performance of this prior art device is satisfactory, but it has

15    the disadvantage that it is very complicated, leading to high manufacturing costs.

UK Patent Application 2,123,291 discloses a sustained release formulation of suloctidil which is a two-part tablet: a first part is a prompt-release portion and a second part is a slow-release portion, which must contain a surface-active agent to promote bio-erosion.

20

US Patent N° 5,393,765 discloses an erodible pharmaceutical composition providing a zero order controlled release profile, comprising low viscosity hydroxypropylmethyl cellulose.

- 25    According to the present invention, there is provided a controlled-release pharmaceutical formulation for oral administration consisting essentially of: an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tableting excipients; and optionally one or more enteric polymers.

- 30    Primarily, "oral administration" means administration to the mouth followed by swallowing. However, the formulations of the present invention may also be administered buccally (i.e. placed behind the top lip and allowed to dissolve), and the term includes such formulations.

"Consisting essentially of" means that at least 95% by weight of the formulation is made up of the listed components. At least 99% by weight of uncoated formulations, and the cores of coated formulations, are preferably made up of the listed components.

- 5 Polymerized ethylene oxide having a number average molecular weight less than 100,000 is sometimes referred to as "polyethylene glycol". However, for simplicity, the term "low molecular weight polyethylene oxide" is used to refer to polymerized ethylene oxide in the number average molecular weight range of interest, namely 15,000 to 750,000.
- 10 Tableting excipients making up formulations according to the invention may be conventional tableting excipients, for example dibasic calcium phosphate, lactose and magnesium stearate.

There are three classes of drug compound which are particularly suitable for administration in formulations according to the invention. The first class is weakly basic compounds. Examples of this class include dipyridamole, noscapine, papaverine, doxazosin, sildenafil and prazosin. Doxazosin and its pharmaceutically acceptable salts are of particular interest.

- 20 The second class are compounds having high solubility in aqueous media. Examples of this class include salbutamol, metoprolol, propranolol, aminophylline, isosorbide mono- and dinitrate, glyceryl trinitrate, verapamil, captopril, diltiazem, morphine, chlorpheniramine, promethazine, eletriptan, darifenacin and fluconazole.

- 25 The third class are compounds having low solubility in aqueous media. Examples of this class include nifedipine, griseofulvin, carbamazepine, felodipine, nimodipine and megestrol.

The terms "high solubility in aqueous media" and "low solubility in aqueous media" will be understood by those skilled in the art. However, the former may be defined as a solubility >1mg/ml in water, and the latter may be defined as a solubility <1mg/ml in water.

- It will be apparent to those skilled in the art that some compounds may fall into more than one of the above classes, for example certain compounds may be weakly basic and have a high solubility in aqueous media.
- 35

Formulations according to the invention have the advantage that they produce a constant rate of release of drugs that are weakly basic and/or have a high solubility in aqueous media in *in vitro* models of the gastrointestinal tract, and so are expected to produce a constant rate of release of the drug in the gastrointestinal tract of a patient. When the drug to be administered has a low solubility in aqueous media, the formulations of the invention have the advantage that they produce a delayed or pulsed release of the drug. However, the formulations are very simple and so can be manufactured at a comparatively low cost.

10

Preferably, the hydroxypropylmethyl cellulose has a number average molecular weight in the range 80,000-250,000. Preferably, the hydroxypropylmethyl cellulose has a degree of methyl substitution in the range 19-30 %. Preferably, the hydroxypropylmethyl cellulose has a degree of hydroxy substitution in the range 4-12 %. A number of hydroxypropylmethyl cellulose polymers are available commercially under the brand name Methocel®, and some of those suitable for use in formulations according to the invention are given in the table below:

15

Methocel® grade	Number average MW	Degree of methyl substitution	Degree of hydroxy substitution	Nominal viscosity of a 2% aqueous solution	USP designation
K4M	89000	19-24%	4-12%	4000cps	2208
K15M	125000	"	"	15000cps	"
K100M	215000	"	"	100000cps	"
E4M	93000	28-30%	7-12%	4000cps	2910
E10M	113000	"	"	10000cps	"
F4M	90000	27-30%	4-7.5%	4000cps	2906

20 Methocel® K4M has characteristics of particular interest.

Preferably, the low molecular weight polyethylene oxide has a number average molecular weight in the range 20,000 to 500,000, more preferably 100,000-300,000. Polyethylene oxide with a number average molecular weight above 100,000 is a powder, which makes it easier to handle than lower molecular weight polyethylene oxide, which has a lower melting point. For example, polyethylene oxide with a number average molecular weight of 6000 has a melting point of 60-63°C.

25

It will be apparent to those skilled in the art that the polyethylene oxide may consist of molecules of different chain lengths, but that the average chain length gives a molecular weight in the range stated. The same applies to the hydroxypropylmethyl cellulose.

- 5 Formulations according to the invention may contain an enteric polymer admixed with the other components of the formulation. In addition or alternatively, formulations according to the invention are preferably provided with a coating of an enteric polymer. Enteric polymers that may be mentioned are phthalate derivatives (including cellulose acetate phthalate, polyvinylacetate phthalate and hydroxypropylmethyl cellulose phthalate),  
10 polyacrylic acid derivatives (including methacrylic acid copolymer), and vinyl acetate and crotonic acid copolymers. Methacrylic acid copolymer is of particular interest.

Preferably, the formulation contains up to 50% by weight of active drug compound, for example 1-20%.

15

It is preferred that the formulations of the invention contain 5-30% by weight of low molecular weight polyethylene oxide, for example 8-10%.

- Preferably, the formulations of the invention contain 10-60% by weight of hydroxypropyl-  
20 methyl cellulose, for example 25-35%.

Formulations having enteric polymer admixed with the other components of the formulation preferably have 10-40% by weight of admixed enteric polymer, for example 25-35%.

- 25 In formulations according to the present invention, it is preferred that the mass ratio of low molecular weight polyethylene oxide:hydroxypropylmethyl cellulose is in the range 2:1-1:5.

- In formulations according to the present invention containing admixed enteric polymer, it  
30 is preferred that the mass ratio of (low molecular weight polyethylene oxide+hydroxypropylmethyl cellulose):admixed enteric polymer is in the range 1:2-6:1, more preferably 1:2-2:1. Preferably, the enteric coating (where present) makes up 2-15% by weight of the formulation, more preferably 5-10% by weight of the formulation.

According to another aspect of the invention, there is provided the use of low molecular weight polyethylene oxide in an oral controlled-release pharmaceutical formulation, having a hydroxypropylmethyl cellulose matrix, to enhance the erosion of the matrix after a predetermined period of time following administration of the formulation to a patient.

- 5 Typically, the predetermined period of time is 6 hours. In this way, a constant rate of drug release can be achieved in the gastrointestinal tract of a patient despite the varying conditions which exist along its length.

By varying the proportion of polyethylene oxide in the formulation it is possible to control  
10 the onset of enhancement of matrix erosion and so the onset of increased drug release following administration of the formulation to a patient.

According to a yet further aspect of the invention, there is provided a process for the production of a pharmaceutical formulation as defined in claim 1, which comprises mixing:  
15 an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tableting excipients; and optionally one or more enteric polymers; followed by pressing into tablets.

The drug release properties of formulations according to the present invention may be  
20 measured in a model of the gastrointestinal tract such as Apparatus 1 of USP 22, page 1578, Method 1 (baskets).

The invention is illustrated by the following examples with reference to the accompanying drawings, in which:

- 25 Figure 1 shows the percentage of drug compound released v time from formulations according to the invention [as prepared in Examples 1(a) and 1(b)] in comparison with a control [as prepared in Example 6] using simple dissolution testing; and  
Figure 2 shows the percentage of drug compound released v time from a formulation according to the invention [as prepared in Example 2(a)] using dissolution testing with first  
30 an acidic and then a neutral dissolution medium.

#### Example 1

##### Sustained release formulations of doxazosin mesylate

(a)

Ingredient	mg/tablet
------------	-----------



Doxazosin mesylate <sup>a</sup>	3.636
Polyethyleneoxide 100,000 MW <sup>b</sup>	9.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	9.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Dibasic calcium phosphate <sup>e</sup>	58.182
Lactose <sup>f</sup>	58.182
Magnesium stearate	2.000
Total	200.000

a equivalent to 3mg doxazosin based on a theoretical activity of 82.5%

b as Polyox® WSR N 10

c as Polyox® WSR N 80

5 d as Methocel® K4M

e as anhydrous

f as lactose fast flo

All of the ingredients except the magnesium stearate were blended together in a Turbula  
 10 blender for 10 minutes. The mixture was then screened using a 30 mesh (500µm  
 apertures) screen and reblended for a further 10 minutes. Then the magnesium stearate  
 was screened through a 30 mesh (500µm apertures) screen and added to the mixture  
 before blending for a further 5 minutes. The blend was then subjected to compression on  
 a tableting machine using 8mm round normal convex tooling to make the required  
 15 number of tablets of 200 mg mass.

(b)

Ingredient	mg/tablet
Doxazosin mesylate <sup>a</sup>	4.876
Polyethyleneoxide 100,000 MW <sup>b</sup>	20.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	20.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Dibasic calcium phosphate <sup>e</sup>	46.562
Lactose <sup>f</sup>	46.562
Magnesium stearate	2.000
Total	200.000

a equivalent to 4mg doxazosin based on a theoretical activity of 82.5%

20 b as Polyox® WSR N 10

c as Polyox® WSR N 80

d as Methocel® K4M

e as anhydrous

25 f as lactose fast flo

200mg tablets were prepared by the method of (a).

(c)

Ingredient	mg/tablet
Doxazosin mesylate <sup>a</sup>	4.876
Polyethyleneoxide 100,000 MW <sup>b</sup>	30.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	30.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Dibasic calcium phosphate <sup>e</sup>	36.562
Lactose <sup>f</sup>	36.562
Magnesium stearate	2.000
Total	200.000

a equivalent to 4mg doxazosin based on a theoretical activity of 82.5%

b as Polyox® WSR N 10

5 c as Polyox® WSR N 80

d as Methocel® K4M

e as anhydrous

f as lactose fast flo

10 200mg tablets were prepared by the method of (a).

### Example 2

Sustained release formulations of doxazosin mesylate containing an enteric polymer

(a)

Ingredient	mg/tablet
Doxazosin mesylate <sup>a</sup>	3.636
Polyethyleneoxide 100,000 MW <sup>b</sup>	9.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	9.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Methacrylic acid copolymer type <sup>e</sup> C	60.000
Dibasic calcium phosphate <sup>f</sup>	28.182
Lactose <sup>g</sup>	28.182
Magnesium stearate	2.000
Total	200.000

15

a equivalent to 3mg doxazosin based on a theoretical activity of 82.5%

b as Polyox® WSR N 10

c as Polyox® WSR N 80

d as Methocel® K4M

20 e as Eudragit® L 100 55

f as anhydrous

g as lactose fast flo

200mg tablets were prepared by the method of Example 1(a).

25

(b)

Ingredient	mg/tablet
Doxazosin mesylate <sup>a</sup>	4.876
Polyethyleneoxide 100,000 MW <sup>b</sup>	20.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	20.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Methacrylic acid copolymer type C <sup>e</sup>	60.000
Dibasic calcium phosphate <sup>f</sup>	16.562
Lactose <sup>g</sup>	16.562
Magnesium stearate	2.000
Total	200.000

a equivalent to 4mg doxazosin based on a theoretical activity of 82.5%

b as Polyox® WSR N 10

c as Polyox® WSR N 80

5 d as Methocel® K4M

e as Eudragit® L 100 55

f as anhydrous

g as lactose fast flo

10 200mg tablets were prepared by the method of Example 1(a).

### Example 3

#### Sustained release formulations of doxazosin mesylate having an enteric coat

(a)

Ingredient	mg/unit
Doxazosin mesylate tablets from Example 1(a)	200.000
Methacrylic acid copolymer type C <sup>a</sup>	6.500
Triethyl citrate	0.650
Talc	3.250
Sodium hydroxide	0.090
Purified Water <sup>b</sup>	(41.510)
Total	210.490

15

a as Eudragit® L 100-55

b Lost during processing and does not appear in the final product

All of the ingredients except the tablets were mixed together until the methacrylic acid  
 20 copolymer had dispersed. This mixture was then applied to the tablets by spraying to  
 give a coating of the required weight using conventional means.

(b)

Ingredient	mg/unit
Doxazosin mesylate tablets from Example 2(a)	200.000

Methacrylic acid copolymer type C <sup>a</sup>	6.500
Triethyl citrate	0.650
Talc	3.250
Sodium hydroxide	0.090
Purified Water <sup>b</sup>	(41.510)
Total	210.490

a as Eudragit® L 100-55

b Lost during processing and does not appear in the final product

5 The tablets were coated by the method of (a).

(c)

Ingredient	mg/unit
Doxazosin mesylate tablets from Example 2(a)	200.000
Methacrylic acid copolymer type A <sup>a</sup>	3.985
Methacrylic acid copolymer type B <sup>b</sup>	3.985
Triethyl citrate	3.984
Ammonia solution <sup>c</sup>	0.058
Water content of ammonia solution <sup>d</sup>	(0.172)
Talc	3.988
Purified Water <sup>d</sup>	(55.554)
Total	216.000

a as Eudragit® L 100

10 b as Eudragit® S 100

c As ammonia solution sp.gr.0.91(25% NH<sub>3</sub>). The aqueous component of this solution is lost during processing.

d Lost during processing and does not appear in the final product

15 The tablets were coated by the method of (a).

#### Example 4

#### Sustained release formulation of darifenacin hydrobromide

Ingredient	mg/tablet
Darifenacin hydrobromide	35.714
Polyethyleneoxide 100,000 MW <sup>b</sup>	20.000
Polyethyleneoxide 200,000 MW <sup>c</sup>	20.000
Hydroxypropylmethylcellulose <sup>d</sup>	60.000
Lactose <sup>e</sup>	62.286
Magnesium stearate	2.000
Total	200.000

- a equivalent to 30mg darifenacin based on a theoretical activity of 84.0%  
 b as Polyox® WSR N 10  
 c as Polyox® WSR N 80  
 d as Methocel® K4M  
 5 e as anhydrous

200mg tablets were prepared by the method of Example 1(a).

#### Example 5

#### 10 Sustained release formulations of fluconazole (suitable for buccal administration)

(a)

Ingredient	mg/tablet
Fluconazole	20.000
Polyethyleneoxide 100,000 MW <sup>a</sup>	10.000
Polyethyleneoxide 200,000 MW <sup>b</sup>	10.000
Hydroxypropylmethylcellulose <sup>c</sup>	30.000
Lactose <sup>d</sup>	29.000
Magnesium stearate	1.000
Total	100.000

- a as Polyox® WSR N 10  
 b as Polyox® WSR N 80  
 15 c as Methocel® K4M  
 d as lactose fastflo

100mg tablets were prepared by the method of Example 1(a).

20 (b)

Ingredient	mg/tablet
Fluconazole	10.000
Polyethyleneoxide 100,000 MW <sup>a</sup>	7.500
Hydroxypropylmethylcellulose <sup>b</sup>	22.500
Dibasic calcium phosphate <sup>c</sup>	34.250
Magnesium stearate	0.750
Total	75.000

- a as Polyox® WSR N 10  
 b as Methocel® K4M  
 c as anhydrous  
 25

100mg tablets were prepared by the method of Example 1(a).

#### Example 6 (Comparative)

Sustained release formulation of doxazosin mesylate not containing polyethyleneoxide

Ingredient	mg/tablet
Doxazosin mesylate <sup>a</sup>	3.636
Hydroxypropylmethylcellulose <sup>b</sup>	60.000
Dibasic calcium phosphate <sup>c</sup>	67.182
Lactose <sup>d</sup>	67.182
Magnesium stearate	2.000
Total	200.000

- a equivalent to 3mg doxazosin based on a theoretical activity of 82.5%  
b as Methocel® K4M  
5 c as anhydrous  
d as lactose fast flo

200mg tablets were prepared by the method of Example 1(a).

#### 10 Example 7

##### Dissolution analysis

The tablets of Examples 1(a), 1(b) and 6 were dissolved using Apparatus 1 of USP 22, page 1578, Method 1 (baskets). The dissolution fluid was 900ml of water at 37°C, the  
15 rotation speed of the baskets was 100 rpm, and the drug compound released was detected by UV spectroscopy at a wavelength of 246 nm. The percentage of drug compound released v time for each tablet type is shown in Figure 1.

The tablets of Example 2(a) were dissolved using Apparatus 1 of USP 22, page 1578,  
20 Method 1 (baskets). The dissolution fluid was 900ml of acidic medium [1M HCl, 100ml; NaCl, 70.2g; water, to 10 litres; pH=2] at 37°C for 2 hours, which was then replaced with neutral pH medium [KH<sub>2</sub>PO<sub>4</sub>, 8.7g; KCl, 47.4g; NaCl, 20.3g; 1M NaOH, 52ml; water, to 10 litres] which was used for the remainder of the experiment. The rotation speed of the baskets was 200 rpm, and the drug compound released was detected by UV spectroscopy  
25 at a wavelength of 246 nm. The percentage of drug compound released v time is shown in Figure 2.

Claims:

1. A controlled-release pharmaceutical formulation for oral administration consisting essentially of: an active drug compound; low molecular weight polyethylene oxide;  
5 hydroxypropylmethyl cellulose; tableting excipients; and optionally one or more enteric polymers.
2. A formulation as claimed in claim 1, wherein the active drug compound is weakly basic.
3. A formulation as claimed in claim 1 or claim 2, wherein the active drug compound is  
10 doxazosin, or a pharmaceutically acceptable salt thereof.
4. A formulation as claimed in claim 1, wherein the active drug compound has a high solubility in aqueous media.
5. A formulation as claimed in claim 1, wherein the active drug compound has a low solubility in aqueous media.
- 15 6. A formulation as claimed in any one of the preceding claims, wherein the hydroxypropylmethyl cellulose has a number average molecular weight in the range 80,000-250,000.
7. A formulation as claimed in any one of the preceding claims, wherein the hydroxypropylmethyl cellulose has a degree of methyl substitution in the range 19-30 %.
- 20 8. A formulation as claimed in any one of the preceding claims, wherein the hydroxypropylmethyl cellulose has a degree of hydroxy substitution in the range 4-12 %.
9. A formulation as claimed in any one of the preceding claims, wherein the polyethylene oxide has a number average molecular weight in the range 20,000-500,000.
10. A formulation as claimed in claim 9, wherein the polyethylene oxide has a number  
25 average molecular weight in the range 100,000-300,000.
11. A formulation as claimed in any one of the preceding claims, wherein an enteric polymer is admixed with the other components of the formulation.
12. A formulation as claimed in any one of the preceding claims, which has a coating containing an enteric polymer.
- 30 13. A formulation as claimed in claim 11 or claim 12, wherein the enteric polymer is methacrylic acid copolymer.
14. A formulation as claimed in any one of the preceding claims, which contains up to 50% by weight of active drug compound.
15. A formulation as claimed in any one of the preceding claims, which contains 5-30%  
35 by weight of low molecular weight polyethylene oxide.

16. A formulation as claimed in any one of the preceding claims, which contains 10-60% by weight of hydroxypropylmethyl cellulose.
17. A formulation as claimed in any one of the preceding claims, which contains 10-40% by weight of enteric polymer by weight admixed with the other components of the  
5 formulation.
18. A formulation as claimed in any one of the preceding claims, wherein the mass ratio of low molecular weight polyethylene oxide:hydroxypropylmethyl cellulose is in the range 2:1-1:5.
19. A formulation as claimed in any one of claims 11-18, wherein the mass ratio of (low  
10 molecular weight polyethylene oxide+hydroxypropylmethyl cellulose): admixed enteric polymer is in the range 1:2-6:1.
20. A formulation as claimed in claim 19, wherein the mass ratio of (low molecular weight polyethylene oxide+hydroxypropylmethyl cellulose): admixed enteric polymer is in the range 1:2-2:1.
- 15 21. A formulation as claimed in any one of claims 12-20, wherein the enteric coating makes up 2-15% by weight of the formulation.
22. A formulation as claimed in claim 21, wherein the enteric coating makes up 5-10% by weight of the formulation.
23. The use of low molecular weight polyethylene oxide in an oral controlled-release  
20 pharmaceutical formulation, having a hydroxypropylmethyl cellulose matrix, to enhance the erosion of the matrix after a predetermined period of time following administration of the formulation to a patient.
24. The use as claimed in claim 23, wherein the predetermined period of time is 6 hours.
- 25 25. A process for the production of a pharmaceutical formulation as defined in claim 1, which comprises mixing: an active drug compound; low molecular weight polyethylene oxide; hydroxypropylmethyl cellulose; tableting excipients; and optionally one or more enteric polymers; followed by pressing into tablets.



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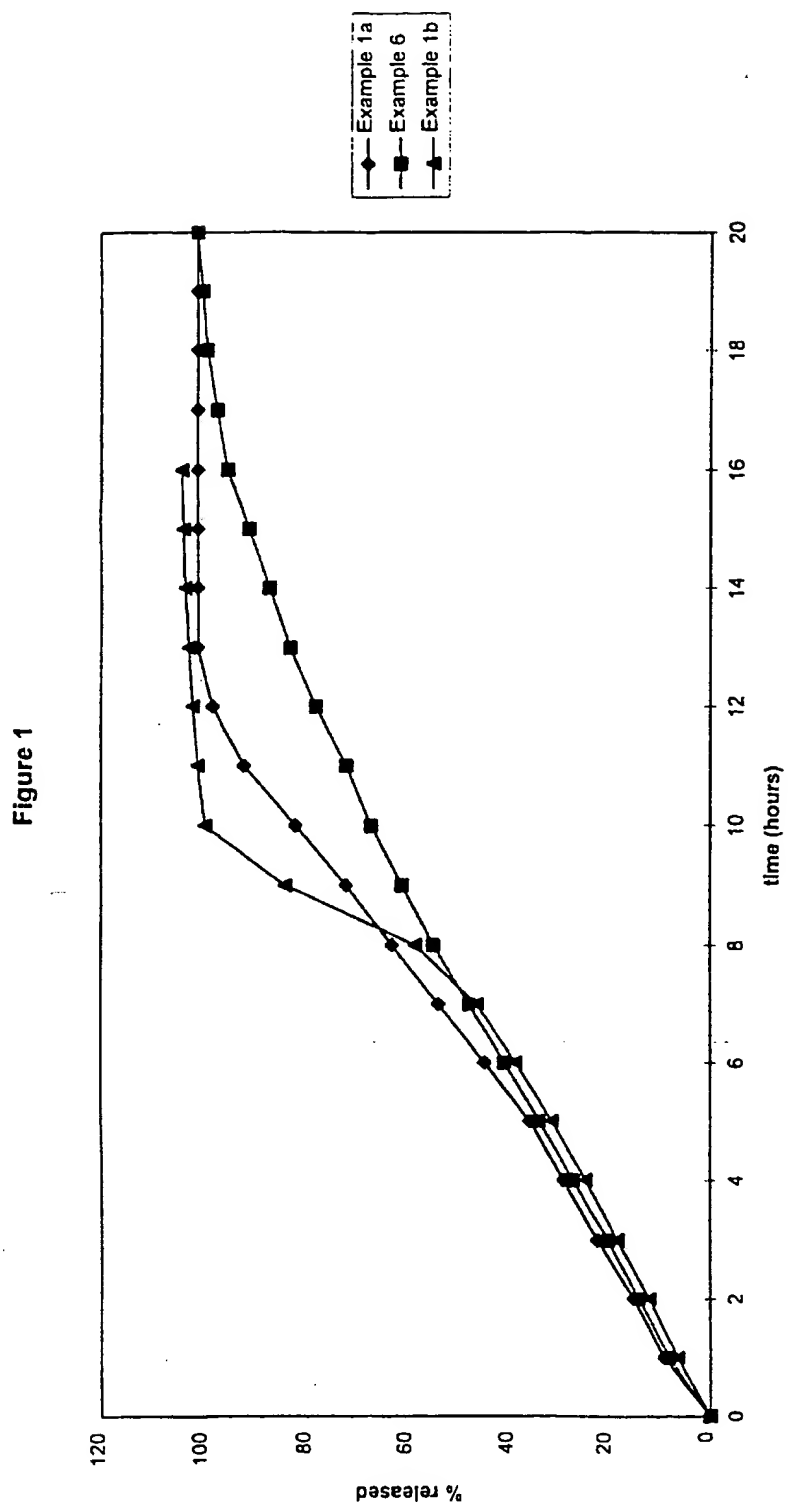
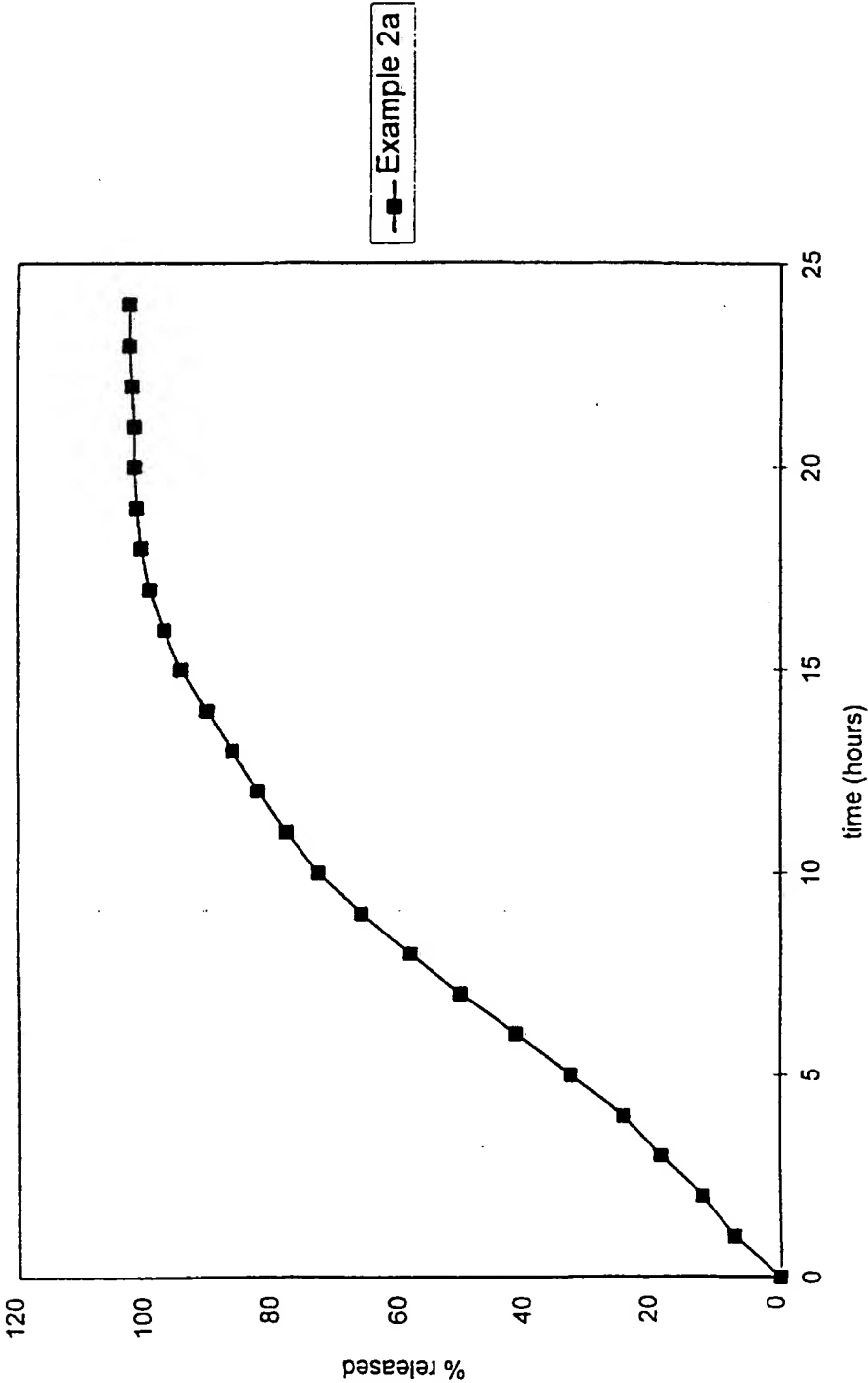


Figure 2



A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/505 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 837 111 A (J.C.DETERS ET AL.) 6 June 1989 see claims see column 17, line 66 - column 18, line 57 see column 20, line 53 - column 21, line 26 see column 21, line 57 - column 22, line 13 ---	1-25
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

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